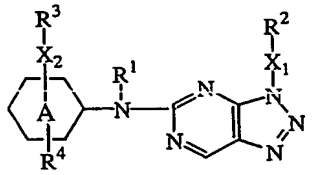
Claims

1. A compound of formula



(I),

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

ring A represents phenyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl;

$R^1$ represents hydrogen; aryl; formyl; $C_{1-6}$alkylcarbonyl; $C_{1-6}$alkyl; $C_{1-6}$alkyloxycarbonyl; $C_{1-6}$alkyl substituted with formyl, $C_{1-6}$alkylcarbonyl, $C_{1-6}$alkyloxycarbonyl, $C_{1-6}$alkylcarbonyloxy; or $C_{1-6}$alkyloxy$C_{1-6}$alkylcarbonyl optionally substituted with $C_{1-6}$alkyloxycarbonyl;

$X_1$ represents a direct bond; $-(CH_2)_{n3}-$ or $-(CH_2)_{n4}-X_{1a}-X_{1b}-$;

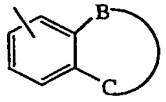
with $n_3$ representing an integer with value 1, 2, 3 or 4;

with $n_4$ representing an integer with value 1 or 2;

with $X_{1a}$ representing O, C(=O) or $NR^5$; and

with $X_{1b}$ representing a direct bond or $C_{1-2}$alkyl;

$R^2$ represents $C_{3-7}$cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula



(a-1)

wherein –B-C- represents a bivalent radical of formula

$-CH_2-CH_2-CH_2-$ (b-1);

$-CH_2-CH_2-CH_2-CH_2-$ (b-2);

$-X_3-CH_2-CH_2-(CH_2)_n-$ (b-3);

$-X_3-CH_2-(CH_2)_n-X_3-$ (b-4);

$-X_3-(CH_2)_{n'}-CH=CH-$ (b-5);

$-CH=N-X_3-$ (b-6);

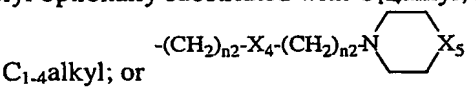
with $X_3$ representing O or $NR^5$;

n representing an integer with value 0, 1, 2 or 3;

n' representing an integer with value 0 or 1;

wherein said $R^2$ substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; $C_{1-6}$alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy,

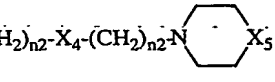
$C_{1-4}$alkyloxy$C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, -C(=O)-$NR^6R^7$, -$NR^5$-C(=O)-$NR^6R^7$, -S(=O)$_{n1}$-$R^8$ or –$NR^5$-S(=O)$_{n1}$-$R^8$; $C_{2-6}$alkenyl or $C_{2-6}$alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, -C(=O)-$NR^6R^7$, -$NR^5$-C(=O)-$NR^6R^7$, -S(=O)$_{n1}$-$R^8$ or –$NR^5$-S(=O)$_{n1}$-$R^8$; polyhalo-$C_{1-6}$alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkyloxy$C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, -C(=O)-$NR^6R^7$, -$NR^5$-C(=O)-$NR^6R^7$, -S(=O)$_{n1}$-$R^8$ or –$NR^5$-S(=O)$_{n1}$-$R^8$; $C_{1-6}$alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, -C(=O)-$NR^6R^7$, -$NR^5$-C(=O)-$NR^6R^7$, -S(=O)$_{n1}$-$R^8$ or –$NR^5$-S(=O)$_{n1}$-$R^8$; polyhalo$C_{1-6}$alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkyloxy$C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, -C(=O)-$NR^6R^7$, -$NR^5$-C(=O)-$NR^6R^7$, -S(=O)$_{n1}$-$R^8$ or –$NR^5$-S(=O)$_{n1}$-$R^8$; $C_{1-6}$alkylthio; polyhalo$C_{1-6}$alkylthio; $C_{1-6}$alkyloxycarbonyl; $C_{1-6}$alkylcarbonyloxy; $C_{1-6}$alkylcarbonyl; polyhalo$C_{1-6}$alkylcarbonyl; cyano; carboxyl; aryloxy; arylthio; arylcarbonyl; aryl$C_{1-4}$alkyl; aryl$C_{1-4}$alkyloxy; $NR^6R^7$; C(=O)$NR^6R^7$; -$NR^5$-C(=O)-$NR^6R^7$; -$NR^5$-C(=O)-$R^5$; -S(=O)$_{n1}$-$R^8$; –$NR^5$-S(=O)$_{n1}$-$R^8$; -S-CN; -$NR^5$-CN; oxazolyl optionally substituted with $C_{1-4}$alkyl; imidazolyl optionally substituted with $C_{1-4}$alkyl; or



with n2 representing an integer with value 0, 1, 2, 3 or 4;
with $X_4$ representing O, $NR^5$ or a direct bond;
with $X_5$ representing O, $CH_2$, CHOH, CH-N($R_5$)$_2$, $NR^5$ or N-C(=O)-$C_{1-4}$alkyl;

$X_2$ represents a direct bond; -$NR^1$-; -$NR^1$-($CH_2$)$_{n3}$-; -O-; -O-($CH_2$)$_{n3}$-; -C(=O)-; -C(=O)- ($CH_2$)$_{n3}$-; -C(=O)-$NR^5$-($CH_2$)$_{n3}$-; -C(=S)-; -S-; -S(=O)$_{n1}$-; -($CH_2$)$_{n3}$-; -($CH_2$)$_{n4}$-$X_{1a}$-$X_{1b}$-; -$X_{1a}$-$X_{1b}$-($CH_2$)$_{n4}$-; –S(=O)$_{n1}$-$NR^5$-($CH_2$)$_{n3}$-$NR^5$-; or –S(=O)$_{n1}$-$NR^5$-($CH_2$)$_{n3}$-;

$R^3$ represents a 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, or a 9-or 10-membered bicyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said $R^3$ substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; $C_{1-6}$alkyl optionally substituted with at least

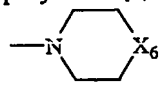
one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkyloxy$C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; $C_{2-6}$alkenyl or $C_{2-6}$alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; polyhalo$C_{1-6}$alkyl; $C_{1-6}$alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; polyhalo$C_{1-6}$alkyloxy; $C_{1-6}$alkylthio; polyhalo$C_{1-6}$alkylthio; $C_{1-6}$alkyloxycarbonyl; $C_{1-6}$alkylcarbonyloxy; $C_{1-6}$alkylcarbonyl; polyhalo$C_{1-6}$alkylcarbonyl; cyano; carboxyl; $NR^6R^7$; $C(=O)NR^6R^7$; $-NR^5-C(=O)-NR^6R^7$; $-NR^5-C(=O)-R^5$; $-S(=O)_{n1}-R^8$; $-NR^5-S(=O)_{n1}-R^8$; -S-CN; $-NR^5-CN$; or  ; and in case $R^3$ represents a saturated or a partially saturated 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, said $R^3$ may also be substituted with at least one oxo;

$R^4$ represents hydrogen; halo; hydroxy; $C_{1-4}$alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^9R^{10}$, $-C(=O)-NR^9R^{10}$, $-NR^5-C(=O)-NR^9R^{10}$, $-S(=O)_{n1}-R^{11}$ or $-NR^5-S(=O)_{n1}-R^{11}$; $C_{2-4}$alkenyl or $C_{2-4}$alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^9R^{10}$, $-C(=O)-NR^9R^{10}$, $-NR^5-C(=O)-NR^9R^{10}$, $-S(=O)_{n1}-R^{11}$ or $-NR^5-S(=O)_{n1}-R^{11}$; polyhalo$C_{1-3}$alkyl; $C_{1-4}$alkyloxy optionally substituted with carboxyl; polyhalo$C_{1-3}$alkyloxy; $C_{1-4}$alkylthio; polyhalo$C_{1-3}$alkylthio; $C_{1-4}$alkyloxycarbonyl; $C_{1-4}$alkylcarbonyloxy; $C_{1-4}$alkylcarbonyl; polyhalo$C_{1-4}$alkylcarbonyl; nitro; cyano; carboxyl; $NR^9R^{10}$; $C(=O)NR^9R^{10}$; $-NR^5-C(=O)-NR^9R^{10}$; $-NR^5-C(=O)-R^5$; $-S(=O)_{n1}-R^{11}$; $-NR^5-S(=O)_{n1}-R^{11}$; -S-CN; or $-NR^5-CN$;

$R^5$ represents hydrogen, $C_{1-4}$alkyl or $C_{2-4}$alkenyl;

$R^6$ and $R^7$ each independently represent hydrogen; cyano; $C_{1-6}$alkylcarbonyl optionally substituted with $C_{1-4}$alkyloxy or carboxyl; $C_{1-6}$alkyloxycarbonyl; $C_{3-7}$cycloalkylcarbonyl; adamantanylcarbonyl; $C_{1-4}$alkyloxy$C_{1-4}$alkyl;

$C_{1-4}$alkyl substituted with $C_{1-4}$alkyl-$NR^5$-; $C_{1-6}$alkyl optionally substituted with at least one substituent selected from halo, hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, polyhalo$C_{1-4}$alkyl, $C_{1-4}$alkyloxy$C_{1-4}$alkyloxy, $NR^{6a}R^{7a}$, $C(=O)NR^{6a}R^{7a}$ or



; with $X_6$ representing O, $CH_2$, CHOH, CH-$N(R_5)_2$, $NR^5$ or N-C(=O)-$C_{1-4}$alkyl;

$R^{6a}$ and $R^{7a}$ each independently represent hydrogen; $C_{1-4}$alkyl or $C_{1-4}$alkylcarbonyl;

$R^8$ represents $C_{1-4}$alkyl optionally substituted with hydroxy; polyhalo$C_{1-4}$alkyl or $NR^6R^7$;

$R^9$ and $R^{10}$ each independently represent hydrogen; $C_{1-6}$alkyl; cyano; $C_{1-6}$alkylcarbonyl; $C_{1-4}$alkyloxy$C_{1-4}$alkyl; or $C_{1-4}$alkyl substituted with $C_{1-4}$alkyl-$NR^5$-;

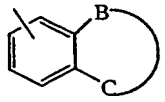
$R^{11}$ represents $C_{1-4}$alkyl or $NR^9R^{10}$;

n1 represents an integer with value 1 or 2;

aryl represents phenyl or phenyl substituted with at least one substituent selected from halo, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{1-6}$alkyloxy, cyano, nitro, polyhalo$C_{1-6}$alkyl or polyhalo$C_{1-6}$alkyloxy.

2. A compound according to claim 1 wherein

$R^2$ represents $C_{3-7}$cycloalkyl; phenyl or a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; or a radical of formula




(a-1)

wherein –B-C- represents a bivalent radical of formula

$-CH_2-CH_2-CH_2-$ (b-1);

$-CH_2-CH_2-CH_2-CH_2-$ (b-2);

$-X_3-CH_2-CH_2-(CH_2)_n-$ (b-3);

$-X_3-CH_2-(CH_2)_n-X_3-$ (b-4);

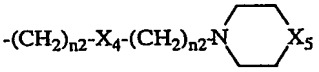
$-X_3-(CH_2)_{n'}-CH=CH-$ (b-5);

with $X_3$ representing O or $NR^5$;

n representing an integer with value 0, 1, 2 or 3;

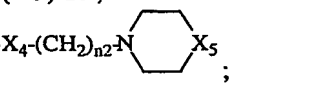
n' representing an integer with value 0 or 1;

wherein said $R^2$ substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; $C_{1-6}$alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$,

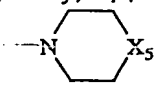
$-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; $C_{2-6}$alkenyl or $C_{2-6}$alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; polyhalo$C_{1-6}$alkyl; $C_{1-6}$alkyloxy optionally substituted with carboxyl; polyhalo$C_{1-6}$alkyloxy; $C_{1-6}$alkylthio; polyhalo$C_{1-6}$alkylthio; $C_{1-6}$alkyloxycarbonyl; $C_{1-6}$alkylcarbonyloxy; $C_{1-6}$alkylcarbonyl; polyhalo$C_{1-6}$alkylcarbonyl; cyano; carboxyl; $NR^6R^7$; $C(=O)NR^6R^7$; $-NR^5-C(=O)-NR^6R^7$; $-NR^5-C(=O)-R^5$; $-S(=O)_{n1}-R^8$; $-NR^5-S(=O)_{n1}-R^8$; -S-CN; $-NR^5-CN$; or 

with n2 representing an integer with value 0, 1, 2, 3 or 4;
with $X_4$ representing O, $NR^5$ or a direct bond;
with $X_5$ representing O or $NR^5$;

$X_2$ represents a direct bond; $-NR^1-$; -O-; -C(=O)-; -C(=S)-; -S-; $-S(=O)_{n1}-$; $-(CH_2)_{n3}-$; or $-(CH_2)_{n4}-X_{1a}-X_{1b}-$;

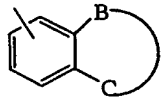
$R^3$ represents a 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said $R^3$ substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; $C_{1-6}$alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; $C_{2-6}$alkenyl or $C_{2-6}$alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; polyhalo$C_{1-6}$alkyl; $C_{1-6}$alkyloxy optionally substituted with carboxyl; polyhalo$C_{1-6}$alkyloxy; $C_{1-6}$alkylthio; polyhalo$C_{1-6}$alkylthio; $C_{1-6}$alkyloxycarbonyl; $C_{1-6}$alkylcarbonyloxy; $C_{1-6}$alkylcarbonyl; polyhalo$C_{1-6}$alkylcarbonyl; cyano; carboxyl; $NR^6R^7$; $C(=O)NR^6R^7$; $-NR^5-C(=O)-NR^6R^7$; $-NR^5-C(=O)-R^5$; $-S(=O)_{n1}-R^8$; $-NR^5-S(=O)_{n1}-R^8$; -S-CN; $-NR^5-CN$; or  ; and in case $R^3$ represents a saturated 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, said $R^3$ may also be substituted with at least one oxo;

$R^5$ represents hydrogen or $C_{1-4}$alkyl;

$R^6$ and $R^7$ each independently represent hydrogen; cyano; $C_{1-6}$alkylcarbonyl; $C_{1-4}$alkyloxy$C_{1-4}$alkyl; $C_{1-4}$alkyl substituted with $C_{1-4}$alkyl-$NR^5$-; $C_{1-6}$alkyl optionally substituted with hydroxy, $C_{1-4}$alkyloxy, $C_{1-4}$alkyloxy$C_{1-4}$alkyloxy, $NR^{6a}R^{7a}$, $C(=O)NR^{6a}R^{7a}$ or  ;

$R^8$ represents $C_{1-4}$alkyl, polyhalo$C_{1-4}$alkyl or $NR^6R^7$.

3. A compound as claimed in claim 1 wherein ring A represents phenyl; $R^1$ represents hydrogen or $C_{1-6}$alkyl; $X_1$ represents a direct bond or -$(CH_2)_{n3}$-; $R^2$ represents $C_{3-7}$cycloalkyl; phenyl; a 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; benzoxazolyl; or a radical of formula

 (a-1)

wherein –B-C- represents a bivalent radical of formula

–$CH_2$-$CH_2$-$CH_2$- (b-1);

-$X_3$-$CH_2$-$(CH_2)_n$-$X_3$- (b-4);

-CH=N-$X_3$- (b-6);

with $X_3$ representing O or $NR^5$;

n representing an integer with value 1;

wherein said $R^2$ substituent, where possible, may optionally be substituted with at least one substituent, in particular with 1 or 2 substituents selected from halo; $C_{1-6}$alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, $C_{1-4}$alkyloxy, $C_{1-4}$alkyloxy$C_{1-4}$alkyloxy, $NR^6R^7$ or -C(=O)-$NR^6R^7$; polyhalo$C_{1-6}$alkyl; $C_{1-6}$alkyloxy optionally substituted with $C_{1-4}$alkyloxy; $C_{1-6}$alkylthio; $C_{1-6}$alkyloxycarbonyl; cyano; arylthio; aryloxy; arylcarbonyl; $NR^6R^7$; $C(=O)NR^6R^7$; -$S(=O)_{n1}$-$R^8$; or imidazolyl optionally substituted with $C_{1-4}$alkyl;

$X_2$ represents a direct bond; -$NR^1$-; -O-$(CH_2)_{n3}$-; -C(=O)-; -C(=O)-$NR^5$-$(CH_2)_{n3}$-; -$(CH_2)_{n3}$-; or –$S(=O)_{n1}$-$NR^5$-$(CH_2)_{n3}$-$NR^5$-; $R^3$ represents a 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said $R^3$ substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; $C_{1-6}$alkyl; or $NR^6R^7$; and in case $R^3$ represents a saturated or a partially saturated 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, said $R^3$ may also be substituted with at least one oxo; $R^4$ represents hydrogen; nitro or carboxyl; $R^5$ represents hydrogen; $R^6$ and $R^7$ each independently represent hydrogen; cyano; $C_{1-6}$alkylcarbonyl optionally substituted with $C_{1-4}$alkyloxy; $C_{1-6}$alkyloxycarbonyl;

$C_{3-7}$cycloalkylcarbonyl; adamantanylcarbonyl; or $C_{1-6}$alkyl; $R^8$ represents $NR^6R^7$; n1 represents an integer with value 2; aryl represents phenyl.

4. A compound as claimed in any one of claims 1 to 3 wherein ring A is phenyl; $R^1$ is hydrogen; $X_1$ is a direct bond or $-(CH_2)_{n3}-$; $R^2$ is indanyl; 2,3-dihydro-1,4-benzodioxanyl; phenyl optionally being substituted with 1 or 2 substituents each independently being selected from $C_{1-6}$alkyl which may optionally be substituted with hydroxy, cyano, $C_{1-4}$alkyloxy, $C_{1-4}$alkyloxy$C_{1-4}$alkyloxy, $NR^6R^7$ or $C(=O)NR^6R^7$; $C_{1-6}$alkyloxy; halo; polyhalo$C_{1-6}$alkyl which may optionally be substituted with hydroxy, cyano, $C_{1-4}$alkyloxy, $C_{1-4}$alkyloxy$C_{1-4}$alkyloxy, $NR^6R^7$ or $C(=O)NR^6R^7$; cyano; $NR^6R^7$; $C(=O)NR^6R^7$; $-S(=O)_{n1}-R^8$; $X_2$ is direct bond; $-NR^1-$; $-O-(CH_2)_{n3}-$; $-C(=O)-$; $-C(=O)-NR^5-(CH_2)_{n3}-$; or $-(CH_2)_{n3}-$; $R^3$ is tetrazolyl; piperazinyl; imidazolyl; oxazolyl; pyrimidinyl; thiazolyl; triazolyl; pyridyl; piperidinyl, pyrazinyl; pyrazolyl or morpholinyl; said rings representing $R^3$ may optionally be substituted with one substitutent selected from $C_{1-6}$alkyl; $NR^6R^7$; hydroxy; halo; and in case $R^3$ represents a saturated or a partially saturated ring system, said $R^3$ may also be substituted with at least one oxo; $R^4$ is hydrogen; $R^6$ and $R^7$ each independently represent hydrogen; cyano; $C_{1-6}$alkylcarbonyl optionally substituted with $C_{1-4}$alkyloxy; $C_{1-6}$alkyloxycarbonyl; $C_{3-7}$cycloalkylcarbonyl; or $C_{1-6}$alkyl; $R^8$ represents $NR^6R^7$.

5. A compound as claimed in any one of claims 1 to 4 wherein the $R^3$ substituent is linked to ring A in meta position compared to the $NR^1$ linker.

6. A compound as claimed in any one of claims 1 to 4 wherein the $R^3$ substituent is linked to ring A in para position compared to the $NR^1$ linker.

7. A compound as claimed in any one of claims 1 to 6 wherein the $R^3$ substituent is an optionally substituted saturated 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N.

8. A compound as claimed in any one of claims 1 to 7 wherein $X_1$ represents a direct bond.

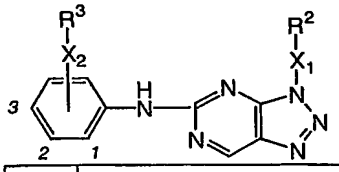
9. A compound as claimed in any one of claims 1, 5 to 8 wherein $R^2$ represents $C_{3-7}$cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula (a-1) wherein said $R^2$ substituent is substituted with at least one substituent selected from

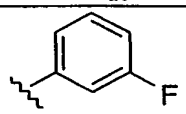
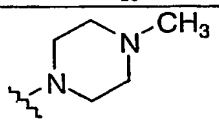
$C_{1-6}$alkyl substituted with $NR^6R^7$; $C_{2-6}$alkenyl or $C_{2-6}$alkynyl, each substituted with $NR^6R^7$; polyhalo$C_{1-6}$alkyl substituted with $NR^6R^7$; $C_{1-6}$alkyloxy substituted with $NR^6R^7$; polyhalo$C_{1-6}$alkyloxy substituted with $NR^6R^7$; or $NR^6R^7$.

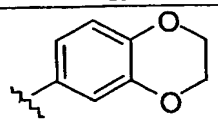
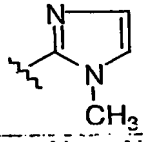
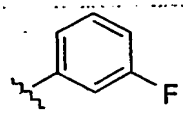
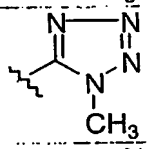
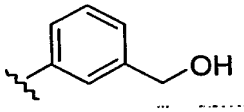
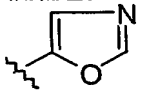
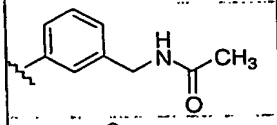
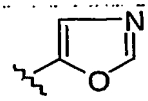
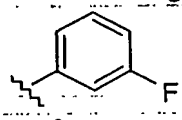
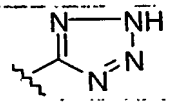
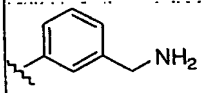
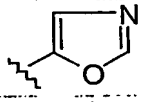
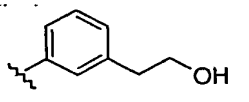
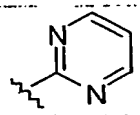
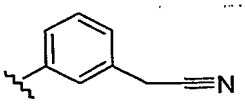
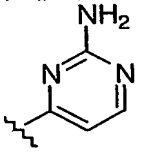
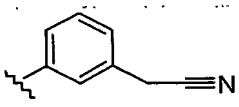
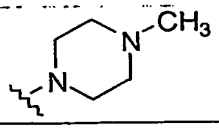
10. A compound as claimed in any one of claims 1, 5, 6, 8 or 9 wherein $R^3$ represents a 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, or a 9-or 10-membered bicyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said $R^3$ substituent is substituted with at least one substituent selected from $C_{1-6}$alkyl substituted with $NR^6R^7$; $C_{2-6}$alkenyl or $C_{2-6}$alkynyl, each substituted with $NR^6R^7$; $C_{1-6}$alkyloxy substituted with $NR^6R^7$; or $NR^6R^7$.

11. A compound as claimed in any one of claims 1, 5, 6, 7, 8 or 10 wherein $R^2$ represents $C_{3-7}$cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula (a-1), wherein said $R^2$ substituent is substituted with at least one substituent selected from halo; polyhalo$C_{1-6}$alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkyloxy-$C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, -C(=O)-$NR^6R^7$, -$NR^5$-C(=O)-$NR^6R^7$, -$S(=O)_{n1}$-$R^8$ or –$NR^5$-$S(=O)_{n1}$-$R^8$; polyhalo-$C_{1-6}$alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, $C_{1-4}$alkyloxy, $C_{1-4}$alkyloxy$C_{1-4}$alkyloxy, $C_{1-4}$alkylcarbonyl, $C_{1-4}$alkyloxycarbonyl, $C_{1-4}$alkylcarbonyloxy, $NR^6R^7$, -C(=O)-$NR^6R^7$, -$NR^5$-C(=O)-$NR^6R^7$, -$S(=O)_{n1}$-$R^8$ or –$NR^5$-$S(=O)_{n1}$-$R^8$.

12. A compound as claimed in claim 1 wherein the compound is selected from

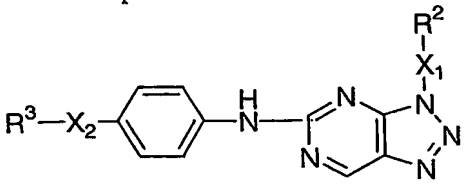


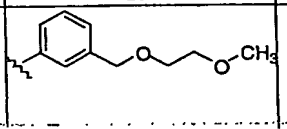
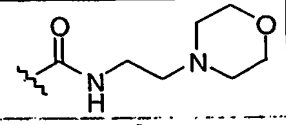
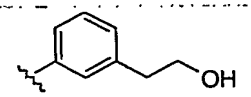
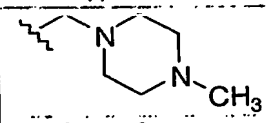
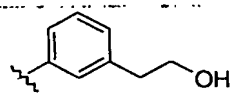
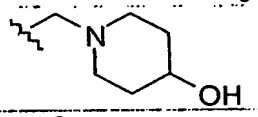
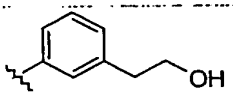
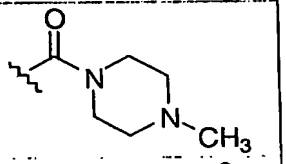
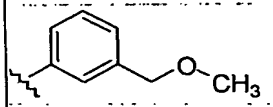
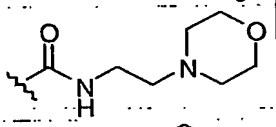
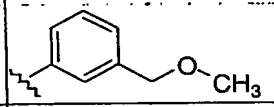
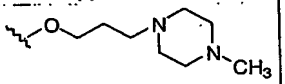
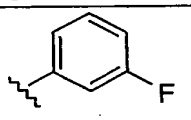
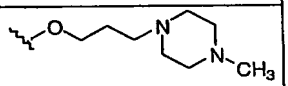
| $X_1$ | $R^2$ | $X_2$ | $R^3$ |
|---|---|---|---|
| db |  | 2-db |  |

| $X_1$ | $R^2$ | $X_2$ | $R^3$ |
|---|---|---|---|
| db |  | 2-db |  |
| db |  | 2-db |  |
| db |  | 2-db |  |
| db |  | 2-db |  |
| db |  | 3-db |  |
| db |  | 2-db |  |
| db |  | 3-NH |  |
| db |  | 2-db |  |
| db |  | 3-db |  |

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

13. A compound as claimed in claim 1 wherein the compound is selected from



| $X_1$ | $R^2$ | $-X_2-R^3$ |
|---|---|---|
| db |  |  |
| db |  |  |
| db |  |  |
| db |  |  |
| db |  |  |
| db |  |  |
| db |  |  |

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

14. A compound as claimed in any one of claims 1 to 13 for use as a medicine.

15. The use of a compound as defined in any one of claims 1 to 13 for the manufacture of a medicament for the prevention or the treatment of diseases mediated through GSK3.

16. The use of a compound as defined in any one of claims 1 to 13 for the manufacture of a medicament for the prevention or the treatment of bipolar disorder (in particular manic depression), diabetes, Alzheimer's disease, leukopenia, FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease), cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy, Pick's disease, Niemann Pick's disease type C, Dementia Pugilistica, dementia with tangles only, dementia with

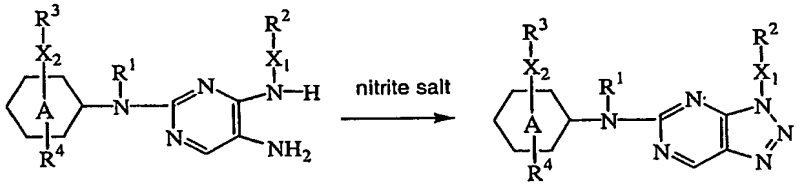
tangles and calcification, Downs syndrome, myotonic dystrophy, Parkinsonism-dementia complex of Guam, aids related dementia, Postencephalic Parkinsonism, prion diseases with tangles, subacute sclerosing panencephalitis, frontal lobe degeneration (FLD), argyrophilic grains disease, subacute sclerotizing panencephalitis (SSPE) ( late complication of viral infections in the central nervous system), inflammatory diseases, depression, cancer, dermatological disorders, neuroprotection, schizophrenia, pain.

17. The use of a compound as claimed in claim 16 for the prevention or the treatment of Alzheimer's disease; diabetes; cancer; inflammatory diseases; bipolar disorder; depression; pain.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 13.

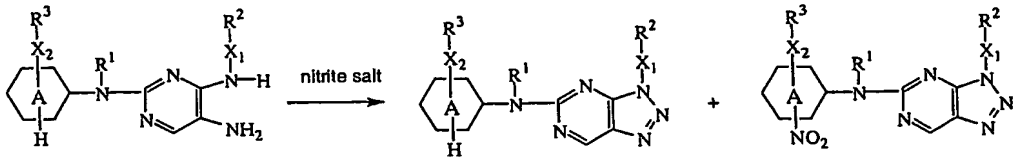
19. A process for preparing a pharmaceutical composition as claimed in claim 18 characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 13 is intimately mixed with a pharmaceutically acceptable carrier.

20. A process for preparing a compound as claimed in claim 1, characterized by
a) cyclizing an intermediate of formula (II) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,




(II) (I)

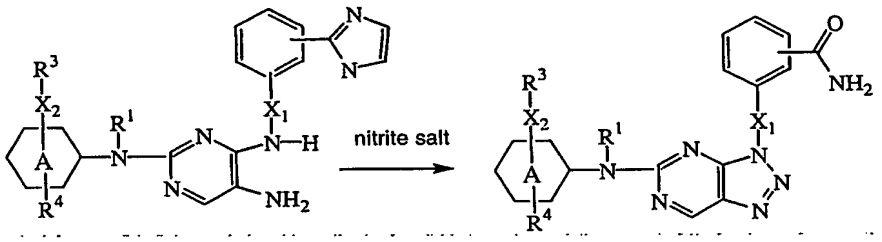
wherein ring A, $R^1$ to $R^4$, $X_1$ and $X_2$ are as defined in claim 1;
b) cyclizing an intermediate of formula (II-a) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,




(II-a) (I-a) (I-b)

wherein ring A, $R^1$ to $R^3$, $X_1$ and $X_2$ are as defined in claim 1;

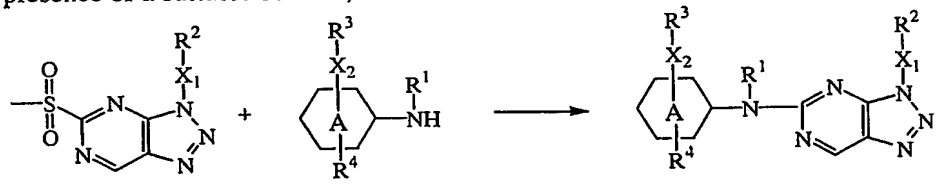
c) cyclizing an intermediate of formula (II-b) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,




(II-b) (I-c)

wherein ring A, $R^1$, $R^3$ and $R^4$, $X_1$ and $X_2$ are as defined in claim 1;

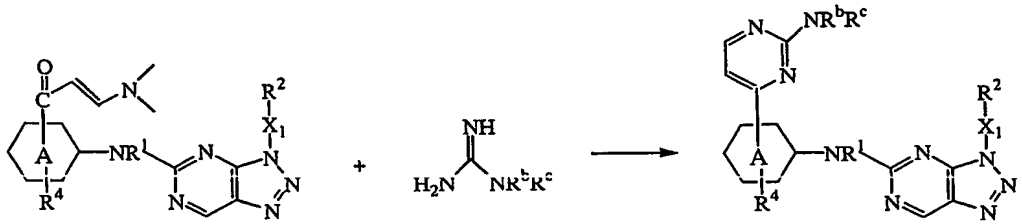
d) reacting an intermediate of formula (III) with an intermediate of formula (IV) in the presence of a suitable solvent,



(III) (IV) (I)

wherein ring A, $R^1$ to $R^4$, $X_1$ and $X_2$ are as defined in claim 1;

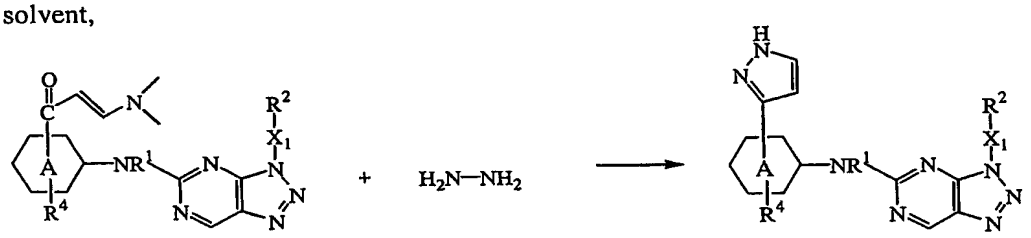
e) reacting an intermediate of formula (XV) with an intermediate of formula (XVI), wherein $R^b$ represents hydrogen, $C_{1-4}$alkyl or cyano, and $R^c$ represents hydrogen or $C_{1-4}$alkyl, in the presence of a suitable solvent and a suitable salt



(XV) (XVI) (I-d)

wherein ring A, $R^1$ $R^2$, $R^4$ and $X_1$ are as defined in claim 1;

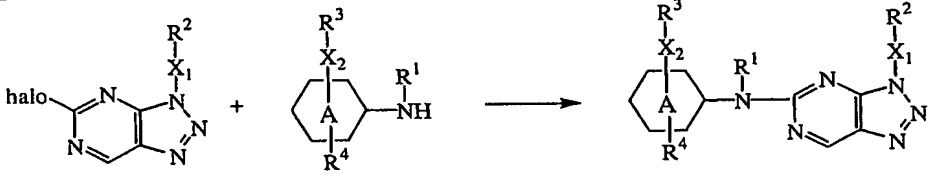
f) reacting an intermediate of formula (XV) with hydrazine in the presence of a suitable solvent,



(XV) (I-e)

wherein ring A, $R^1$ $R^2$, $R^4$ and $X_1$ are as defined in claim 1;

g) reacting an intermediate of formula (III') with an intermediate of formula (IV) in the presence of a suitable solvent, and optionally in the presence of a suitable base,



(III') (IV) (I)

wherein ring A, $R^1$ $R^2$, $R^3$, $R^4$, $X_1$ and $X_2$ are as defined in claim 1;

or, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, quaternary amines or *N*-oxide forms thereof

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